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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,690	08/28/2003	Joanne Young Hee Kwak Kim	112461-016	9043

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/651,690	KIM ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-283* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 28-40, 43-69, 73-82, 86-111, 113-137, 139-163, 165-175, 177-187, and 277-283* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 20-27,41,42,70-72,83-85,112,138,164,176 and 188-276.

DETAILED ACTION

1. Applicant's response and amendment received September 2, 2005 is acknowledged.

Applicant has indicated that claims 278-287 in the claim set submitted on December 27, 2004 were inadvertently omitted, and this omission was not found by the examiner prior to issuing a first action on the merits on March 29, 2005. Applicant is thanked for attempting to clarify the record by indicating in the reply that claims 1-293 are pending and that claims 278-287 have not been entered. However, this is incorrect since claims that are not entered cannot be considered pending, and further, claims 278-287 were never previously presented. As such, the numbering of claims in response to the office action mailed March 29, 2005 is not accordance with 37 C.F.R. 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 CFR 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Given that claims 278-287 were never presented they cannot be indicated as not entered, and therefore misnumbered claims 288-293 have been renumbered as 278-283. This renumbering of the claims should be reflected in any claim sets submitted by applicant in response to the instant office action.

It is also noted that some of the rejections set forth in the office action mailed

March 29, 2005 rejected claims that were not present in the case at that time. The examiner would like to apologize for not picking up on the claim numbering discrepancy. The inclusion of claims that did not exist into the rejections was inadvertent and does not materially affect the grounds of rejection that were set forth.

Claims 1-283 are pending in the case.

Claims 1, 53, 73, 86, 112, 113, 130, 131, 139, 156, 157, 165, 177, and 277 have been amended.

Claims 278-283 are renumbered as explained above.

Claims 20-27, 41, 42, 70-72, 83-85, 112, 138, 164, 176, and 188-276 stand withdrawn as per the office action mailed March 29, 2005.

Claims 1-19, 28-40, 43-69, 73-82, 86-111, 113-137, 139-163, 165-175, 177-187 and 277-283 are under examination in the instant office action.

Response to Amendment

2. The declaration filed on September 2, 2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the prior art reference of Pluenneke (of record).

The declaration is ineffective for many reasons. First, the evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Pluenneke reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Specifically, Dr. Kwak-Kim has stated that she conceived of the invention prior to April 19, 1999, but no demonstrative evidence, such as copies of a laboratory notebook, or evidence of disclosure to another, such as through a grant application submitted for funding, have been submitted to support this position. See MPEP 715.07. Second, the evidence submitted is insufficient to establish diligence from a date prior to the date of reduction to practice of the Pluenneke reference to either a constructive reduction to practice or an actual reduction to practice since no facts to establish diligence have been provided other than the statement by Dr. Kwak-Kim in paragraph 10 of her declaration stating that she was diligent. See MPEP 715.07(a). Third, the declaration does not indicate that the acts of Dr. Kwak-Kim relied upon to antedate the art of Pluenneke was carried out in this country, a NAFTA country, or in a WTO member country. See MPEP 715.07(c). Fourth, the application has multiple inventors, yet the declaration is signed only by Dr. Kwak-Kim. What contribution did the other named inventors make to the claimed invention? When and where did they make these contributions, and were the other inventors diligent? If all the named inventors contributed to the claimed invention,

all inventors must sign the declaration. See MPEP 715.04. If the other named inventors did not contribute to the claimed invention, the inventorship must be amended in compliance with 37 CFR 1.48(b).

For all of the reasons above, the declaration submitted September 2, 2005 is ineffective to obviate any and all art rejections based upon the teachings of Pluenneke.

Claim Objections

3. The objection to claim 82 has been obviated by applicant's amendment to the claim to correct an error in dependency.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19, 28-40, 43-52 and 277 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, is maintained for the reasons of record set forth in the office action mailed March 29, 2005.

Applicant's arguments filed September 2, 2005 have been fully considered but they are not persuasive. Applicant has amended base claim 1 to clarify the claimed method and supply missing information. However, claim 1 and all its dependent claims

are still unclear. Claim 1 now recites that the Th1/Th2 ratio is to be measured and that the administration of a compound (either a Th1 antagonist or a Th2 agonist) reduces the Th1/Th2 ratio. It is not clear if the measurement is taken before or after administration of the compound. If the measurement is taken before administration, how does this information aid a physician in deciding between the administration of a Th1 antagonist or a Th2 agonist? Is there a ratio at which the physician should not administer any compound? If the ratio is measured subsequent to administration of the compound, how can efficacy be assessed since no pretreatment ratio was measured as a basis of comparison? Are pre- and post-administration measurements required? Additionally, as currently recited, the claims require the in serum or intracellular immune responses to be measured *in the subject.* Typically, and in accord with the specification examples and teachings of the instant specification, Th1 and Th2 responses are determined by removing a sample from a patient (whole blood or serum) and then subjecting that sample to *in vitro* diagnostic methodologies such as flow cytometry, ELISAs, ELISPOTs and Western blotting. As such the measuring step does not actually occur *in the subject.* Amending the claim to indicate that a blood sample is taken from a subject and that this sample is tested for the presence and amount of Th1 and Th2 cytokines either in serum or through intracellular cytokine staining of PBMCs would clarify how to practice the claimed method.

6. The rejection of claims 38-40, 67-69, 80-82, 139-163, 165-175, 177-187, and 291-293 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention due to the recitation of "D2E7", "CDP571", or "CDP870" as the sole means of identifying the TNF-α antagonist used in the claimed method has been withdrawn due to applicant's persuasive arguments.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The rejection of claims 38-40, 67-69, 80-82, 139-163, 165-175, 177-187, and 291-293 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn since the sequence of antibody D2E7 is completely disclosed in US Patent 6,090,382, the sequence of CDP571 is completely disclosed in US Patent 5,994,510, and the sequence of CDP870 is completely disclosed in US 2002/0151682 A1.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The rejection of claims 1, 12-15, 28-31, 33, 35, 43, 44, 49, 53, 56, 61, and 73 under 35 U.S.C. 102(b) as being anticipated by Chaouat et al. (J. Immunol., 1995, 154:4261-4268, see entire document, of record) has been withdrawn due to applicant's amendment to the claims to include additional limitations.

11. The rejection of claims 1, 12, 14, 28-32, 35, 43, 44, 49, 53, 56, 61, and 73 under 35 U.S.C. 102(b) as being anticipated by Chaouat (Cell Immunol., 1994, 157:328-340, see entire document, of record) has been withdrawn due to applicant's amendment to the claims to include additional limitations.

12. The rejection of claims 1, 12, 14, 28-30, 31, 33-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 113, 116-118, 121, 125-126, 139, 142-44, 147, 151-153, 165, 168-170, 173, and 174 under 35 U.S.C. 102(e) as being anticipated by

Pluenneke (US 2001/0021380 A1, see entire document, of record) has been withdrawn due to applicant's amendment to the claims to include additional limitations.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. The rejection of claims 1, 12, 28, 35, 37, 40, 53, 69, 73, 82, 177, 180-183, and 186 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Athwal et al. (US 2002/0151682 A1, see entire document) has been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

15. Claims 86, 103-111,113, 129-137, 139, and 155-163 stand rejected and claims 53, 56-58, 61, 65-68, 73, 76-81, 89-91, 94, 98-100, 116-118, 121, 125-126, 142-44, 147, 151-153, 165, 168-170, 173, and 174 as amended on September 2, 2005 are rejected under 35 U.S.C. 103(a), as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) for the reasons of record set forth in paragraph 17 of the office action mailed March 29, 2005.

Pluenneke discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and paragraphs 8 and 9). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Pluenneke include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies including, but not limited to, infliximab, D2E7, and CDP571 (see particularly paragraphs 19, 20, and 32). These reagents are to be used in treating disorders of the human female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly paragraph 73). It should be noted that methods that inhibit spontaneous abortion or infertility inherently enhance the ability of a subject to carry an embryo to term. Suitable dosages and routes of administration for the reagents disclosed by Pluenneke are provided (see particularly paragraphs 26-32). Note the reagents can be administered once or multiple times (see particularly paragraph 29). The disclosed dosage ranges for etanercept and

the anti-TNF-α monoclonal antibodies overlap with the ranges claimed by applicant, and these agents can be injected intravenously, intramuscularly, subcutaneously, or can be administered as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly paragraph 26). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).

Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they also have an inherent Th1 to Th2 ratio. The teachings of Pluenneke provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods inherently alter the Th1 to Th2 ratio present in the subject being treated. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.

Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. only specify IVIg and not a specific Ig isotype, but the most abundant isotype in blood plasma is IgG, and as such Coulam et al. inherently teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the

paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al. indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67). Indeed, Coulam et al. specifically state that initiating immunotherapy preconceptually as compared with postconceptually offers the advantage of significantly increase live birth rates (see particularly the first full sentence of the left column of page 68).

Both Pluenneke and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer just the TNF-α antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-α antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving

a successful conception and pregnancy, and that doing so significantly increases live birth rates. Therefore, initiating treatment with a TNF-α antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure as evidenced by an increased live birth rate.

Applicant has argued that this rejection should be withdrawn in light of the declaration under 37 CFR 1.131 of Dr. Kwak-Kim which attempts to remove the teachings of Pluenneke as prior art. As discussed above, the declaration is ineffective and as such the rejection is maintained.

16. The rejection of claims 1, 53, 73, 86, 101, 102, 113, 127, 128, 139, 154, 165, 175, and 277-292 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) has been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

17. The rejection of claims 177, 187, and 293 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Athwal et al (US 2002/0151682 A1, see entire document, of record) as applied to claims 1, 12, 28, 35, 37, 40, 53, 69, 73, 82, 177, 180-183, and 186 above, and further in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) has

been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

18. The rejection of claims 1, 5, 6, 12, 14, and 16-19 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) has been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

19. The rejection of claims 1, 2-4, 7-9, 46-48, 50-55, 58-60, 62-64, 73-75, 86-88, 91-93, 95-97, 113-115, 118-120, 122-124, 139-141, 144-146, 148-150, 165-167, and 170-172 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed 5/19/2004, see entire document) as applied to claims 1, 5, 6, 12, 14, and 16-19 above, and further in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document, of record) has been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

20. The rejection of claims 177-179, 182, 184, and 185 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Athwal et al (US 2002/0151682 A1, see entire document, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed 5/19/2004, see entire document) as applied to claims 1, 5, 6, 12, 14, and 16-19 above, and in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document, of record) has been withdrawn due to applicant's amendment of the base claims to include the limitation "prior to conception".

The following are new grounds of rejection necessitated by Applicant's amendment to the claims received September 2, 2005.

21. Claims 53, 56, 61, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaouat et al. (J. Immunol., 1995, 154:4261-4268, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record)

Chaouat et al. disclose multiple methods that increase the number of successful pregnancies in the CBA x DBA/2 mouse strain that is significantly prone to spontaneous abortions (also referred to as fetal resorption in the text, see particularly the title and the

Materials and Methods subsection Fetal resorption) as compared to CBA x BALB/c controls (see entire document, particularly the abstract). Chaouat et al. measure cytokines from *in vitro* cultured cells and disclose that in normal pregnancies Th2 responses are predominant in comparison to Th1 responses, but that CBA x DBA/2 mice show increased levels of the Th1 cytokines IL-2, INF-γ, and TNF-α and are deficient in the Th2 cytokines IL-4 and IL-10 relative to control mice (see particularly the paragraph that spans pages 4261 and 4262, the first full paragraph of page 4262, the first paragraph of the results section on page 4263, and Figure 1). Th1 cytokine responses can be suppressed, and spontaneous abortion can be prevented, in these mice by the administration of recombinant IL-10 protein (which antagonizes the activity of INF-γ and TNF-α), the administration of a neutralizing monoclonal antibody that binds INF-γ, the administration of pentoxifillin (a compound that inhibits the production of TNF-α, thus making it a TNF-α antagonist) and the administration of recombinant ovine trophoblastin (see particularly Figures 3, 5, 6, the paragraph that spans pages 4263 and 4264, the first two full paragraphs of page 4265 and the last full paragraph of page 4266). The administration of recombinant IL-10 directly enhances the level of Th2 cytokines in the subject. The mice used in the experiments were allowed to mate, and as such they experienced a natural conception (see particularly the Materials and Methods section). The teachings of the prior art differ from the claimed invention in that the interventions performed by Chaouat et al. to inhibit spontaneous abortions did not occur prior to conception.

Coulam et al. teach that live birth rates are significantly increased when immunotherapy was begun preconceptually compared with postconceptually (see entire document, particularly the first full sentence in the left column of page 68).

Therefore, a person of ordinary skill in the art ant the time the invention was made would have been motivated to perform the immunotherapeutic inventions taught by Chaouat et al. prior to conception as was taught by Coulam et al. to gain the advantage of significantly increased birth rates as was taught by Coulam et al.

22. Claims 53, 56, 61, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaouat (Cell Immunol., 1994, 157:328-340, see entire document) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record).

Chaouat teaches the prevention of embryo resorptions in the spontaneous abortion prone mouse model CBA x DBA/2 through the administration of a neutralizing polyclonal rabbit anti-TNF antiserum and thought the administration of pentoxyfillin, a compound that suppresses the production of TNF (see particularly the abstract, the second paragraph of the introduction, the paragraph that spans pages 334 and 335, and the second full paragraph on page 338). These treatments are able to suppress the Th1 cytokine TNF-α in these mice. Inhibition of spontaneous abortion inherently enhances birth rates and the ability of an animal to carry an embryo to term. Pregnancy in the experimental mice was determined by the observation of a vaginal plug and as such a natural conception occurred by the mating of the mice. All animals have an

immune system, and as such they inherently have a ratio of Th1 to Th2 responses. The teachings of the prior art differ from the claimed invention in that the administrations performed by Chaouat et al. did not occur prior to conception.

Coulam et al. teach that live birth rates are significantly increased when immunotherapy was begun preconceptually compared with postconceptually (see entire document, particularly the first full sentence in the left column of page 68).

Therefore, a person of ordinary skill in the art ant the time the invention was made would have been motivated to perform the immunotherapeutic compound administrations taught by Chaouat et al. prior to conception as was taught by Coulam et al. to gain the advantage of significantly increased live birth rates as was taught by Coulam et al.

23. Claims 69, 82, 177, 180-183, and 186 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record).

The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that Pluenneke

does not disclose the anti-TNFα monoclonal antibody CDP870 as part of his non-limiting examples of anti-TNFα antibodies that are suitable for use in methods of treating infertility and spontaneous abortion.

Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of Pluenneke with modified timing of administration as taught by Coulam et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in the methods of Pluenneke et al. as modified by Coulam et al. since CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

24. Claims 101, 102, 127, 128, 154, 175, and 278-282 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record).

The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) as taught by Pluenneke and

modified by the teachings of Coulam et al. and Janeway et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

25. Claims 187 and 283 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 53, 56-58, 61, 65-69, 73, 76-82, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, 174, 177, 180-183, and 186 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record).

The teachings of Pluenneke, Coulam et al., Janeway et al. and Athwal et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 187 and 283 in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3.

Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke and Athwal et al. that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) with the timing of administration modified by the teachings of Coulam et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

26. Claims 1, 5, 6, 12, 14, 16-19, 28-31, 33-39, 43-46, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document).

The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. In summary, these teachings indicate that all women suffering from

disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-α antagonists, and that treatment is most effective when it begins prior to conception. These teachings differ from the claimed invention in that they do not disclose the measurement of the Th1 to Th2 ratio in patients being treated for spontaneous abortions or infertility.

Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-γ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble antigen (see particularly the materials

and methods section) or alternatively, the cytokines were measured directly from patient sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as taught by Raghupathy et al. before performing the therapeutic methods of Pluenneke as modified by Coulam et al. Motivation to incorporate this method step comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer

spontaneous abortion of immunological etiology into the treatment method taught by Pluenneke as modified by Coulam et al. would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such interventions.

27. Claims 40, 69, 82, and 177, 180-183, and 186 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) as applied to claims 1, 5, 6, 12, 14, 16-19, 28-31, 33-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record).

The teachings of Pluenneke, Coulam et al., Janeway et al., and Raghupathy et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP870.

Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long

plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of Pluenneke with modified timing of administration as taught by Coulam et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in the methods of Pluenneke et al. as modified by the teachings of Coulam et al. and Raghupathy et al. since CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

28. Claims 277 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) as applied to claims 1, 5, 6, 12, 14, 16-19, 28-31, 33-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-

163, 165, 168-170, 173, and 174 above, and further in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record).

The teachings of Pluenneke, Coulam et al., Janeway et al. and Raghupathy et al. have been discussed above. These teachings differ from the claimed invention as in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke et al. that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) with the timing of administration modified by the teachings of Coulam et al. and Raghupathy et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

29. Claims 2-4, 7-9, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, 122-124, 140, 141, 145, 146, 148-150, 166, 167, 171, 172, 178,

179, 184, and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 1, 5, 6, 12, 14, 16-19, 28-31, 33-40, 43-46, 49, 53, 56-58, 61, 65-69, 73, 76-82, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, 174, 117, 180-183, and 186 above, and further in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document).

The teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al. and Athwal et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 2-4, 7-9, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, 122-124, 140, 141, 145, 146, 148-150, 166, 167, 171, 172, 178, 179, 184, and 185 in that they do not disclose measuring the Th1 to Th2 cytokine ration using absolute cell counts or by intracellular cytokine staining. These teachings also do not explicitly indicate the treatment of the patients that have undergone assisted reproductive technologies such as *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls

(see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute the cytokine detection methods and patient populations taught by Ng et al. for the detection methods and patients taught collectively by the teachings of Pluenneke, Coulam et al., Raghupathy et al., and Athwal et al. Motivation to make these substitutions comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Pluenneke that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

30. No claims are allowable.

31. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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